Claims

1. A bispecific molecule that comprises a first binding domain which binds cell surface membrane-bound heat shock protein (Hsp) and a second binding domain which binds a member of the anti-apoptotic Bcl-2-associated athanogene (Bag) family.

2. The bispecific molecule of claim 1, wherein said Hsp is Hsp70.

3. The bispecific molecule of claim 1 or 2, wherein said Bag is Bag-4.

4. The bispecific molecule of any one of claims 1 to 3, wherein said first and second binding domain bind to the C-terminal domain of the Hsp and Bag protein, respectively.

5. The bispecific molecule of any one of claims 1 to 4 that is a bispecific immunoglobulin, wherein the first binding domain is a first immunoglobulin variable region, and the second binding domain is a second immunoglobulin variable region.

6. The bispecific molecule of any one of claims 1 to 5, which is a single chain or a dimeric or multimeric molecule.

7. The bispecific molecule of any one of claims 1 to 6, which has at least one further functional domain.

8. The bispecific molecule of any one of claims 1 to 7, which is a bispecific antibody.

9. A nucleic acid molecule or a composition of nucleic acid molecules encoding the bispecific molecule of any one of claims 1 to 8.

10. The nucleic acid molecule or composition of claim 9, wherein any one of said nucleic acid molecules is operably linked to expression control sequences.

11. A cell transformed with the nucleic acid molecule or composition of claim 9 or 10.

12. The cell of claim 11, which expresses the bispecific molecule on the cell surface.

13. The cell of claim 11 or 12, which is a natural killer (NK) cell.

14. A method for producing a bispecific molecule of any one of claims 1 to 8 comprising cross-linking a first and second binding domain as defined in any one of claims 1 to 4, and optionally a further functional domain.

15. The bispecific molecule of claim 7 or 8, or the method of claim 14, wherein said further functional domain is a cytotoxic agent or a label.

16. A method for producing a bispecific molecule of any one of claims 1 to 8 or 15 comprising culturing the cell of claim 11 or 12 under appropriate conditions and isolating the bispecific molecule or portions thereof.

17. A composition comprising in one or more compartments, the bispecific molecule of any one of claims 1 to 8 or 15, the nucleic acid molecule or composition of claim 9 or 10 or the cell of any one of claims 11 to 13; and optionally a pharmaceutically acceptable carrier.

18. The composition of claim 17 for use in diagnosis, prophylaxis, vaccination or therapy.

19. Use of the bispecific molecule of any one of claims 1 to 8 or 15, the nucleic acid molecule or composition of claim 9 or 10, the cell of any one of claims 11 to 13 or an antibody capable of recognizing membrane-bound Bag or a corresponding binding molecule, a nucleic acid molecule encoding said antibody or binding molecule, or a cell expressing said antibody or binding molecule for the preparation of a pharmaceutical composition for the targeting and/or treatment of a tumor or an infectious disease.

20. Use of a nucleic acid molecule of claim 9 or a nucleic acid molecule encoding an

antibody capable of recognizing membrane-bound Bag or a corresponding binding molecule in a form suitable for expression of the bispecific molecule on the cell surface for the preparation of a pharmaceutical composition for the targeting of a cell to a tumor cell or to a cell infected by a pathogen.

21. A method of treating a tumor or infectious disease in a mammal comprising administering to the mammal a therapeutically effective dose of a bispecific molecule of any one of claims 1 to 8 or 15 or a compound capable of recognizing membrane-bound Bag.

22. A method for diagnosing a radiation therapy resistant neoplastic disorder or infectious disease of a patient comprising assaying membrane-bound Bag and/or co-localization of Hsp and Bag protein as defined in any one of claims 1 to 4 on the cell surface of cells in a sample from the patient, wherein the presence or increased amount of membrane-bound Bag and/or co-localized Hsp and Bag protein is indicative for the disorder.

23. Use of NK cells or an activator of NK cells for the preparation of a pharmaceutical composition for the treatment of a tumor or infectious disease in a patient which has been positively tested according to the method of claim 22.

24. The use of claim 23, wherein said NK cells are activated prior to administration to the patient or are designed to be administered in conjunction with an activator of NK cells.

25. The use of claim 22 or 23, wherein said activator comprises a peptide of Hsp70 and/or a peptide of Bag protein.

26. Use of Bag protein or fragment thereof or an agent mimicking membrane-bound Bag in association with Hsp for the preparation of a pharmaceutical composition for inducing and/or enhancing a cytolytic attack of NK cells against undesired cells.

27. The use of claim 26, wherein said agent induces or enhances the expression and/or localization of Bag on the cell surface of said undesired cell.

28. The use of claim 26 or 27, wherein said agent or a combination of agents induce or enhance concomitantly the expression and/or co-localization of Hsp and Bag on the cell surface of a tumor cell.

29. The use of claim 26, wherein said agent is comprised of at least one of the following: Hsp70 and/or Bag-4 polypeptides or fragments thereof, cells expressing Hsp70 in association with Bag-4 on their cell surface, the membrane-fraction of cells expressing Hsp70 in association with Bag-4 on their cell surface and/or anti-idiotypic antibodies of membrane-bound Hsp70 in association with Bag-4.

30. The use of any one of claims 26 to 29, wherein said pharmaceutical composition additionally contains at least one compound which enhances an immune response.

31. The use of any of claims 26 to 30, wherein said undesired cells are tumor cells.

32. A method for the preparation of an agent mimicking membrane-bound Hsp70 in association with Bag-4 comprising the following steps:
    (a) raising antibodies specific for membrane-bound Hsp70 in association with Bag-4; and
    (b) raising anti-idiotypic antibodies by using the antibodies of step (a) or at least part of the variable region thereof as an antigen.

33. The method of claim 32, wherein the anti-idiotypic antibody is humanized.

34. Use of an inhibitor of the association of membrane-bound Hsp70 with a member of the anti-apoptotic Bcl-2-associated athanogene (Bag) family for the preparation of a pharmaceutical composition for the treatment of a tumor.

35. The use of claim 34, wherein said inhibitor binds to the ATPase domain of Hsp and/or to the corresponding binding domain of Bag.

36 The use of claim 34 or 35, wherein said inhibitor is selected from the group consisting

of an antibody, an aptamer, small molecules, a peptide and a peptidomimetic.

37. The use of any of claims 23 to 25, 31, or 34 to 36, wherein said tumor or neoplastic cell growth is a radiation therapy resistant tumor.

38. Use of an inhibitor as defined in any one of claims 34 to 37 as a first agent for the preparation of a pharmaceutical composition for sensitizing tumor cells for the activity of a cytotoxic second agent.

39. The use of claim 38, wherein said second agent is an apoptosis inducing agent.

40. The use of claim 38 or 39, wherein said second agent is a chemotherapeutic drug or γ-irradiation.

41. The use of any one of claims 38 to 40, wherein said second agent is selected from the group consisting of staurosporine, mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, dacarbazine, chlorambucil, etoposide, mitoxantrone, genestein, phenoxodiol, interferons, drugs triggering death receptors such as the CD95, or pro-drugs or pharmaceutically acceptable salts of any one thereof.

42. The use of any one of claims 38 to 41 comprising the use of a second agent as defined in any one of claims 38 to 41 for the preparation of a pharmaceutical composition for the treatment of a tumor, wherein if said first agent and second agent are comprised in a first and second pharmaceutical composition, said first and second pharmaceutical composition being applicable simultaneously or sequentially.

43. The use of any one of claims 34 to 42, wherein said pharmaceutical composition is designed to be administered prior, during or after exposure of the tumor cells to γ-irradiation.

44. The use of any one of claims 19, 20, 23 to 25, 34 to 43 or the method of claim 21, wherein said tumor is a carcinoma of colon, pancreas, head/neck, cervix or

glioblastoma.

45. A method for the identification of an anti-tumor agent comprising:
(a) providing a cell expressing Hsp70 and Bag-4 on its cell surface;
(b) treating said cell with at least one candidate compound; and
(c) determining whether said candidate compound interferes with the association of Hsp70 and Bag-4 on the cell surface of the cell.

46. The method of claim 45, wherein said at least one compound is provided as a library of compounds.

47. The method of claim 45 or 46, wherein said at least one compound is an antibody, a polypeptide, and/or a small molecule.

48. An anti-tumor agent identified by the method of any one of claims 45 to 47.

49. A kit for use in a method of any one of claims 22 or 45 to 47, said kit comprising an anti-Hsp and/or anti-Bag antibody; and optionally suitable means for detection.

50. The use of any one of claims 19, 20, 25 to 31, the method of claim 21 or the kit of claim 49, wherein said Bag protein is Bag-4.

51. The use of any one of claims 19, 20, 25 to 31 or 50, the method of claim 21 or 50 or the kit of claim 49 or 50, wherein said Bag protein fragment thereof comprises at least one epitope of the C-terminal localized BAG domain.

52. Use of an antibody specifically recognizing membrane-bound Bag protein or a binding domain thereof for the detection and/or treatment of a tumor or an infectious disease.

53. The use of claim 52, wherein said antibody or binding domain bind to an epitope of the C-terminal localized BAG domain.

54. The use of claim 52 or 53, wherein said Bag protein is Bag-4.

55. The use of any one of claims 52 to 54, wherein said antibody or binding domain comprises a further functional domain as defined in claim 15.